"ANTHISAN" IN TREATMENT OF ASTHMA AND HAY-FEVER

BY

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The unpredictable fluctuations which are a feature of the clinical course of asthma, together with the dauntless optimism with which asthmatics invariably welcome any new remedies, have always made clinical evaluation of these a matter of great difficulty. The very large number of initially encouraging reports of numerous different remedies in the past, now often totally abandoned, point reproachfully to the ease with which both doctor and patient are frequently mistaken in their estimate of the benefit conferred by the new preparation. It should be the duty of those who are interested in the treatment of asthma to assess as accurately as possible each new remedy, not only to protect practitioners and prevent disappointment to the long-suffering asthmatics themselves, but also to allow subsequent investigations of further new substances to proceed unhampered by erroneous and confusing estimates of the benefits of their immediate predecessors.

Reports from France and America on the clinical use of the new antihistamine substances (antergan, neonantergan, "benadryl," pyribenzamine) agree that good or even excellent results are obtained in the treatment of rhinitis, both seasonal and perennial; that markedly beneficial results follow the use of the drugs in various forms of urticaria and in some other dermatoses; that pruritus ani and vulvae and the pruritus of atopic dermatitis are often relieved and drug rashes benefited. Results in the treatment of asthma, however, are less certain.

Nevertheless enough has been published to encourage the belief that antihistamines do confer benefit in many cases of asthma, as Table I shows. From perusal of the American and French literature on antihistamines it is abundantly clear, however, that enough care has not always been taken to eliminate from the clinical trials those factors which contribute to erroneous clinical impressions. It is likely that herein lies the explanation of the otherwise irreconcilable variation in the apparent efficacy of these remedies in the hands of different workers.

TABLE I.—*A Selection of Results with Benadryl in the Hands of Different American Workers*

Author	Asthma (Seasonal)		Asthma (Perennial)	
	No. of Cases	No. Improved	No. of Cases	No. Improved
Levin (1946)	—	—	87	57
Waldbott (1946)	30	14	48	24
Koelsche, Prickman, and Carryer (1945)	19	14	12	4
Blumenthal and Rosenberg (1946)	—	—	12	4
McElin and Horton (1945)	—	—	3	1
Eyermaun (1946)	—	—	4	3
Feinberg and Friedlaender (1946)	—	—	16	0

In most of the published reports on the antihistamines, especially in the treatment of asthma, clinical data are conspicuous by their absence. When authors write of their patients "deriving benefit," this statement is seldom amplified in any way, nor are the criteria of improvement indicated. In many cases the duration of the trial is not stated, nor, apparently, is the use of a control preparation thought to be necessary. These faults appear more plainly evident in those series in which the authors claim a high degree of improvement with antihistamines. To take a single instance, Levin (1946) reports the results of benadryl in the treatment of no fewer than 87 asthmatics, of whom

as many as 67% of the children and 65% of the adults "obtained relief." Apart from stating that benefit was less in those patients who had a cold, the author gives no information at all about the patients; nor is this example an isolated instance.

The Present Investigation

In this investigation an attempt has been made to assess as accurately as possible the effect of one of the antihistamine preparations in asthma and hay-fever. In order to eliminate those factors which tend to create erroneous impressions, the patients have been very carefully selected and critically observed both while taking the trial preparation itself and while taking an inert dummy preparation of identical appearance. So that the criteria of success or failure with the trial preparation should not consist entirely of verbal descriptions of patients' subjective sensations, a system of numerical grading of the severity of the symptoms has been adopted, with the object of obtaining a graphic expression of the effect of the trial preparation itself as opposed to the effect of the control.

The compound used in this trial has been one of the newest and most active of the antihistamine substances—namely, pyranisamine maleate ("anthisan"), which is chemically N-dimethylaminoethyl - N - P-methoxybenzyl- α -amidopyridine acid maleate, otherwise called neoantergan maleate. It is a colourless crystalline solid, soluble in water. The preparation has been kindly supplied by Messrs. May and Baker put up in 0.1-g. tablets, coloured green, together with 0.1-g. tablets of identical appearance but composed of quite inert substances—namely, sucrose 50 g., lactose 350 g., starch 100 g.

Each patient has, unknown to him, received a quantity of the inert preparation alternating with the real substance. The initial dosage of both the inert and the real has been one tablet (0.1 g.) thrice daily. This has been increased to three tablets thrice daily after three days on the initial smaller dose. Patients suffering from nocturnal asthmatic attacks have also received 0.3 g. immediately before retiring at night.

The patients have been chosen from among those attending the Asthma Research Clinic at Guy's Hospital during 1946 and 1947. All have been under my direct observation.

Asthma Cases

The asthmatic patients comprised a mixed group of cases of different ages, sex, and duration, of various degrees of severity, with only one feature in common—namely, that all were examples of allergic as opposed to bronchitic asthma, with minimal infection and lung damage. However, although cases of primary bronchitic asthma were excluded from the trial, in the cases of very long standing there was bound to be emphysema and some degree of associated bronchial infection.

Twenty-five patients (12 male, 13 female) were included in the trial (Table II). Their ages ranged from 9 to 48 years. Most had perennial asthma, but some had seasonal exacerbations during June and July, over which period part of the trial was carried out. Of these patients 20 were well known at the clinic, and were particularly suitable for study, as either their asthma periodicity was regular or their symptoms were continually present. The remaining five were new patients with comparatively short histories, included in order to observe the effect of the preparation upon cases of recent onset. Cases 19 and 24 were excluded from the trial owing to the unexpected, startling, and sustained improvement that was produced by the inert control tablets.

The 20 patients had had a great deal of treatment both at Guy's and elsewhere. During the period of the trial it was not found practicable to withhold all other forms of treatment, and therefore, with the exception of the five new cases (Nos. 13, 21, 25, 26, 27), all the patients were instructed to continue with any palliative treatment to which they were

accustomed. The five new patients received the test substances only, and no other form of treatment. If they had been taking occasional ephedrine tablets these were withheld.

TABLE II.—*Asthma Cases*

Case No.	Age	Sex	Occupation	Duration of Symptoms
1	48	F	Housewife	40 years
2	48	F	"	22 "
3	31	F	"	12 "
4	30	F	"	21 "
5	41	F	"	18 "
6	28	M	Mechanic	6 "
7	37	M	Clerk	7 "
8	20	F	Housewife	17 "
9	19	F	Seamstress	2 "
10	27	M	Unemployed	2 "
11	33	M	Clerk	7 "
12	33	M	Fitter	1 year
13†	10	M	School	3 months
14	35	M	Clerk	30 years
15	29	F	Housewife	2 "
16	28	M	Independent	1 year
17	24	F	Typist	16 years
18	39	M	Clerk	2 "
19*	22	F	Journalist	4 "
20	41	F	Factory worker	5 "
21†	25	M	Clerk	9 months
22	31	M	Agent	2 years
23	11	M	School	6 months
24*	49	F	None	42 years
25†	18	F	Student	3 months
26†	9	M	School	8 "
27†	22	F	Typist	3 years

* Excluded from the trial. † Patients new to the clinic.

Hay-fever Cases

The hay-fever patients numbered 15 (Table III). All were skin-tested by the scratch technique and all were found to be sensitive to grass pollens. Cases 3, 9, and 14 were also sensitive to tree pollens. Four patients had asthma as well as hay-fever, but were not included in the asthma series as the unstable periodicity of their attacks made grading impossible. All the 15 cases had definite seasonal periodicity. Cases of perennial rhinitis were not included.

TABLE III.—*Hay-fever Cases*

Case No.	Age	Sex	Occupation	Pollen	Start of Symptoms	Start of Trial
1	21	F	None	Grass	June 1	June 8
2	24	M	Medical student	"	May 29	" 5
3	14	F	School	Grass and tree	June 4	" 11
4	22	M	Medical student	Grass	May 20	" 2
5	39	M	Storekeeper	"	" 25	" 11
6	15	M	School	"	June 2	" 9
7	33	M	Traveller	"	" 11	" 18
8	28	F	Housewife	"	May 22	" 5
9	21	M	Mechanic	Grass and tree	" 14	May 21
10	27	M	Clerk	Grass	" 16	" 23
11	36	M	Farmer	"	June 1	June 7
12	12	F	School	"	" 1	" 7
13	34	F	Housewife	"	May 18	May 25
14	32	M	Doctor	Grass and tree	June 14	June 21
15	40	M	Clerk	Grass	May 16	May 23

Scheme of Trial and Methods of Assessment

Asthma

Grading.—All the patients in the asthma group were graded according to the severity of their symptoms in the past (Table IV). The system adopted was similar to that recommended by the Asthma Research Council (Committee on Assessment of Results in Asthma). In the present series,

TABLE IV.—*Grading of Asthmatic Patients*

Present Series	Asthma Research Council	Symptoms
Grade 6	Grade I	Continual asthma. Patients who are unable to work at all or go to school
Grade 5	Grade II	Continual asthma. Patients who are able to work or go to school 75% of the time
Grade 4	—	Continual asthma. Patients able to work or go to school, but wheezy on at least one occasion during each 24 hours
Grade 3	Grade III	Patients whose attacks occur at least once a week
Grade 2	Grade IV	Patients whose attacks occur at least once a month
Grade 1	Grade V	Patients whose attacks occur less than once a month

however, an additional grade has been included, and it has also been found convenient to reverse the grading numbers, so that Grade 1 represents the mildest type of case instead of the most severe.

Method.—The period of the trial for asthmatic patients extended over eight weeks, about half of which was spent on the active preparation, and the remainder, unknown to the patient, on the inert dummy tablets. For the first two weeks the dummies were used, after which the active preparation was substituted. After some weeks on the active preparation, patients returned to the dummies for a week or two before continuing with the active preparation. If a patient appeared to be showing a sustained improvement on the active preparation he was usually changed to the inert dummies.

At the start of the trial the patient was graded according to his past asthmatic history. At the end of each successive week of the trial he was regraded according to the severity of his symptoms during the preceding week. At the end of the eight-weeks period the average weekly grading number while taking the active preparation was available for comparison with the average weekly grading figure while taking the dummies. When the whole series of asthmatic patients had been investigated their average individual weekly grading numbers on the active preparation were added together for comparison with the sum total of the same figures whilst on the dummies (Table V).

TABLE V.—*Summary of Results in Asthma Cases*

Case No.	Grade Before Trial	Weekly Grade Nos.								Average Grade Nos. (Weekly)		
		1st	2nd	3rd	4th	5th	6th	7th	8th	U	D	R
1	6	6D	6D	6R	6R	6R	6R	6D	6R	6	6	6
2	5	5D	5D	4R	3R	3D	5R	5D	5R	5	4.5	4.2
3	5	5D	5D	5R	5R	5D	5R	—	5R	5	5	5
4	6	6D	6R	6D	6R	—	—	—	—	6	6	6
5	5	5D	5D	4R	5R	4D	5R	4R	5R	5	4.6	4.5
6	3	3D	3D	4R	2R	3R	4R	3D	3R	3	3	3.2
7	4	4D	4D	4R	4R	5R	5R	—	—	4	4	4.5
8	3	2D	2D	2R	2R	2R	3R	3R	3R	3	2	2.3
9	3	3D	3D	3R	3R	3R	3D	3D	3R	3	3	3
10	4	4D	4D	3R	3R	4R	4D	4D	3R	4	4	3.2
11	5	4D	4D	4R	3R	2R	2D	4R	5	3.3	3.2	3.2
12	5	4D	3D	3R	4D	4D	3R	4R	4R	5	3.7	3.5
13	4	4R	4R	4D	3D	3R	3D	3D	4R	4	3.2	3.7
14	4	4D	4D	3R	3R	4D	3R	3R	4D	4	4	3
15	3	3D	3D	3R	3R	3R	3D	2D	2R	3	2.7	2.7
16	3	3D	3D	3R	3R	3R	3D	3D	3D	3	3	3
17	3	3D	3D	3R	2R	3R	3D	3D	3R	3	3	2.7
18	3	3D	3D	4R	3R	2R	3D	3D	3R	3	3	3
19*	4	3D	2D	2D	2D	2D	4U	4U	2D	4	2.1	—
20	3	3D	2D	2R	2R	3D	3R	2D	2R	3	2.5	2.2
21	4	4R	4R	3D	3D	3D	4D	3R	3R	4	3.2	3.5
22	3	4D	3D	3R	2R	3R	3R	3D	3D	3	3.2	2.7
23	4	3D	3D	3R	3R	3R	3R	3D	3D	3	3	3
24*	4	3D	2D	2D	3U	3D	2D	4U	3D	3.5	2.5	—
25	4	3D	2D	2R	4R	3R	3D	4D	3R	4	3	3
26	4	3D	3D	3R	4R	3R	4D	3R	3D	4	3.2	3.2
27	4	4D	3R	2R	3R	4D	3R	3R	4D	4	4	2.8
Total grade nos. for whole series										99.0	90.1	87.1
Average weekly grade nos. for whole series										4	3.6	3.5

* Not included in trial. U = Untreated. D = Dummy. R = Real.

It is not intended that any statistical significance should be attached to these figures. The grading numbers serve as convenient numerical symbols representative of the degree of severity of the asthma of each patient week by week. The figures, however, do bear a definite fixed relation to the severity of the symptoms, so that the sum total of the average weekly grading numbers for the whole group on the real, as opposed to the inert, preparation may be taken as a reflection of the summation of the severity of the asthma of all the 25 patients while taking neoantergan, compared with the severity of their symptoms while they were not.

Hay-fever

Grading.—The symptoms of hay-fever patients have been divided into four grades according to the severity—i.e., Grade 4, severe symptoms; Grade 3, moderate symptoms; Grade 2, slight symptoms; Grade 1, no symptoms.

Method.—A scheme similar to that used for the asthma patients has been devised for the hay-fever patients. Owing to the comparatively short duration of the symptoms in some

cases the period of time on the dummy tablets has been curtailed to a week in most instances, while that on the active preparation has ranged from four to seven weeks. The results are shown in Table VI.

TABLE VI.—*Summary of Results in Hay-fever Cases*

Case No.	Weekly Grade Nos. Results	Average Weekly Grade Nos.		
		Untreated (u)	Dummy (d)	Real (r)
1	4u4d2r2r1r ..	4	4	1.8
2	4u4d3r2r1r2r ..	4	4	1.8
3	4u4d3r1r2r ..	4	4	2
4	3u3d2r1r3d1r1r ..	3	3	1.2
5	4u4d1r4d1r1r ..	4	4	1
6	4u4d3r2r1r1r1r ..	4	4	1.4
7	4u4d1r1r ..	4	4	1
8	4u2r2r3d2r ..	4	3	2
9	4u4d1r4d1r1r1r ..	4	4	1
10	4u4d3r3r2r2r ..	4	4	2.4
11	4u4d1r2r1r1r ..	4	4	1.2
12	3u3d2r2r3d1r1r ..	3	3	1.5
13	4u4d2r2r4d2r2r ..	4	4	2
14	3u1r1r3d1r ..	3	3	1
15	4u4d3r2r4d2r2r2r ..	4	4	2.2
Total ..		57	56	23.5
Average for series ..		3.8	3.73	1.5

Discussion

Before this investigation began a few cases of asthma and hay-fever had been treated with neoantergan, with apparently extremely disappointing results in the former and very encouraging results in the latter condition. The tentative impression of the powers of this drug thus created has been confirmed in striking manner by the more detailed observations on the series of cases summarized above.

In the asthmatic group the average of the weekly grading figures for the 25 patients observed over 105 weeks while taking neoantergan was 3.5. The equivalent figure for the same 25 patients observed for 89 weeks on the control tablets was 3.6, and before treatment was started the figure was 4. In other words, there appeared to be no appreciable difference in the severity of the symptoms while taking the drug, as opposed to the control tablets.

In contrast to the asthmatics, the severity of the symptoms of the 15 hay-fever patients while taking the preparation over a period of 69 weeks was indicated by the figure 1.5, whereas the severity of the symptoms of these patients observed over 21 weeks on the controls was indicated by the figure 3.7—a very striking contrast indeed.

These graphic expressions of results strongly reinforce the clinical impression of the benefit of the drug in this series—namely, that in asthma neoantergan appears to be of little or no value, whereas in hay-fever the symptoms have been partially or completely controlled in all the patients who were taking the preparation, including a number with severe symptoms.

The necessity for using a control preparation in an investigation of this kind is illustrated by asthma cases Nos. 19 and 24. Both these patients showed a great improvement in their asthma as soon as they began to take the dummy tablets, and not only was the improvement sustained throughout the period of the trial but both patients became worse when the dummy tablets were withheld. Case 24 was of particular interest, as this patient had previously been a severe asthmatic in Grade 4—a case of very many years' standing—and was also suffering from atopic dermatitis, which, however, remained unaltered in spite of the improvement in the asthma.

Even before this trial it was considered improbable that neoantergan would prove capable of influencing materially the severe asthmatics of Grades 5 and 6. It was to be hoped, however, that some of the patients with milder degrees of asthma might show some improvement—for example, those with only a moderate degree of daily or

nocturnal wheeziness or those who suffered from one or two mild attacks of short duration weekly. The published reports of other workers led me to expect some improvement in patients of this kind, but none was forthcoming which could with justification be ascribed to neoantergan; in fact, improvement in Grades 3 and 4 appeared just as likely to occur with the control as with the real preparation, and in any event was usually fluctuant and variable. For example, asthma patient No. 2, a severe case, had two good weeks as soon as she went on to the real preparation; but this improvement persisted even when the control was substituted, and when she finally did relapse the previous degree of improvement could not again be achieved with the active preparation.

It did not seem that a short duration of the patient's history favourably influenced the results with neoantergan. Asthma cases Nos. 13, 21, 23, 25, and 26 had all had asthma for less than a year, but none showed any improvement—in fact, Cases 13 and 21 actually appeared to be worse during treatment. Neither did the youth of this particular group of patients impart any salutary effect.

In spite of its soporific effect neoantergan conferred no apparent benefit upon patients whose asthma showed a nocturnal periodicity. For example, asthma case No. 7, a young clerk, had an attack every night with clockwork regularity, usually at about 3 to 4 a.m. This had persisted even during treatment as an in-patient, and sleeping by day instead of by night made no difference, the asthma again occurring some five hours after retiring to rest. This man received a large dose of neoantergan as a preventive immediately before getting into bed, but the attacks occurred just the same. Nor did the drug appear to exert any appreciable effect in relieving the established attack, which, however, invariably responded to adrenaline. It was of particular interest to note that after the trial was over Cases 16, 18, 20, 21, and 26 improved at once on adrenaline, which they had not previously taken, except occasionally. The improvement was sufficient to move Cases 21 and 26 down a grade as soon as they had mastered the technique of self-injection of adrenaline.

In addition to the object-lesson of Cases 19 and 24, both of whom did so well on the inert control tablets, another point of interest emerges from the grading results—namely, that the patients' grading figures (3.6) during the trial while taking the dummies were considerably lower than the figures (4) for the same cases before the trial, in spite of careful assessment of the grades based on previous observation of the individual patients over periods of time ranging from several months to several years. It is easy to see how, if a control preparation had not been used, such a change in symptoms could be mistaken for an improvement due to the test drug.

There can be no doubt at all of the value of neoantergan in the symptomatic treatment of hay-fever. In addition to the striking changes in the grading figures while taking the preparation (1.5) compared with the figures on the dummies (3.7), the patients themselves were unanimous in their praise of the preparation, although disappointed during periods on the dummy tablets. Some of these patients had had pollen-desensitization courses in the past, several of them more than once. They declared that neoantergan conferred as much protection as any but the most successful desensitization course. Two patients, not included in the trial, were treated with a high degree of success with neoantergan, which was started half-way through the season when their pre-seasonal desensitization course was found to be not wholly effective.

Side-effects.—Of the 42 patients reported in this trial side-effects were noted in 23—10 had slight nausea, 6 nausea and drowsiness, 4 drowsiness, 1 impotence, and 2 giddiness.

Conclusions

Neoantergan conferred no apparent benefit upon 25 specially selected and carefully observed asthmatic patients.

Neoantergan was markedly successful in reducing the severity of the symptoms of 15 cases of hay-fever.

When working with asthmatic patients an erroneous impression of the efficacy of a new preparation is likely to be formed unless a very careful scheme of trial is planned, preferably using a control preparation.

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CHIASMA LESION DUE TO FALL IN EPILEPTIC FIT

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Damage to the optic nerve due to a fall in an epileptic fit is surprisingly rare, although optic-nerve lesions may follow slight head injuries. Chiasmal damage occurring after epileptic seizures has not been previously recorded in the literature. The following case, which ended in optic atrophy and blindness in one eye, is of special interest because of its unusual course and visual-field changes.

Case Report

The patient, a single man aged 32, suffered from epilepsy, probably of traumatic origin. Generalized fits followed a severe head injury sustained six years before. These recurred at intervals of one to two months, with sudden falls and no aura. At the end of November, 1944, he fell on his forehead during a fit. There was a swelling over the right eye due to extravasation of blood. He was confused for the rest of the day—as usual after his seizures. Next day, when mentally clear, he complained of blindness in his right eye. Examination revealed a complete loss of vision in this eye, and a marked temporal-field defect of the left eye with normal visual acuity. This was evident in subsequent examinations. Simple and stereoscopic x-ray examination of the skull immediately afterwards did not show any fracture.

About a fortnight after the accident there was a distinct difference in the two disks, the right being paler. After a month there was an obvious atrophy of the right disk, with paleness, narrowing of the large retinal arteries, and reduction of the small vessels. This condition was still unchanged when a complete examination of fundus, visual field, and acuity was carried out in May, 1945, six months after the accident. Since further developments were not anticipated no regular examinations were made. On July 17, 1945, however, the patient reported that a few days previously he had begun to see again with the right eye and that vision had gradually improved. Immediate examination showed a central scotoma in his right

eye with full peripheral visual fields. The visual acuity for finger-counting was 3 ft. (0.91 metre). An examination two days later showed that the central scotoma had disappeared and that the acuity had risen to 6/9. The visual field in the left eye still showed some temporal defect, but to a less degree than in the first period after the accident.

On Aug. 2 he reported that the sight of the right eye had again become worse, and attributed this to an injury inflicted by a patient, who he alleged threw lumps of soil into his face. He also stated that a few days previously he had had to bend his head while helping with weeding in the garden. The visual field two days later showed a central scotoma and a concentric constriction of the peripheral field; the visual acuity had fallen to 1/60. Subsequent examinations showed that the scotoma gradually increased in size, the peripheral field became more and more restricted, leaving eventually a pericentral annular island of vision, and within a week the patient was again blind in the right eye. The visual field of the left eye showed no definite temporal defect during this phase. The direct pupillary reaction to light in the right eye was from the beginning of the observation sluggish and poor, decreasing in the first week after the accident until it became fairly stable after the atrophy of the optic nerve had been established. No definite change was noted during the short spell of recovery. Up to January, 1948, no further change has occurred; the right eye remains blind, with atrophy of the disk; the left eye shows full visual field and normal acuity. The direct light reaction, though very poor, is still obtainable.

Discussion

Complete blindness and optic atrophy of the right eye after a fall in an epileptic fit, and a temporal-field defect of the left eye, pointed to a lesion in the chiasmal region affecting the fibres of the right optic nerve and the nasal retinal fibres from the left eye. This type of injury has been repeatedly discussed in the literature. The skull fracture which often accompanied such lesions suggested a direct traumatic damage to the nerve, and specimens have been shown in which the nerve in this section had actually been torn. Early writers were mainly concerned with the possible types of skull injury which might produce this nerve damage. Various mechanisms have been suggested (Liebrecht, 1912; Coppez, 1929; Rand, 1937), but more recent experience has made it clear that bone injury and anatomical nerve lesions are not the only cause of the traumatic chiasma syndrome, and that vessel damage alone may have the same effect and produce the initial symptoms (Traquair, 1933, 1942; Dandy, 1932; Rodger, 1943; Hughes, 1943). Rodger differentiates bleeding into the sheaths and subvagal and intraneural haemorrhages.

There can be little doubt that in our patient there was a vascular lesion; the remission and subsequent relapse cannot be explained in any other way. The fact that central vision was the last to return when the recovery took place, and that a central scotoma was the first symptom when the relapse occurred, seems to indicate an intraneural damage. The onset immediately after the injury is in favour of traumatic rupture of the vessel wall, with consequent intraneural haemorrhage (Rodger, 1943). This would also account for the relapse. After a slight injury the vessel, which had been closed, started to leak again, causing a gradually increasing extravasation—a mechanism well recognized in meningeal and brain-vessel damage, when a minor incident may cause renewed extravasation long after the initial trauma.

With regard to the progress of our case the changes during the first few weeks after injury were as anticipated. It is the general experience that a visual-field defect and loss of visual acuity occur immediately after the injury, while atrophy of the optic nerve usually appears within four weeks. In seven cases of optic-nerve lesions Rodger (1943) noted an average interval of 17 days, the shortest